REMARKS

Claims 1-10 and 12-52 are currently pending in the present application. Applicant notes that the "Remarks" section of the previous response incorrectly identified the added claims as "45-49" rather than "45-52." Since claims 50-52 depend indirectly from claim 27, applicant assumes that the enablement and written description (new matter) rejections made by the Examiner apply to these claims as well.

Applicant thanks the Examiner for identifying the typographical errors in the specification. Some of the requested amendments to the specification are believed to correct these errors. The other requested amendments to the specification are made to put the application in compliance with the sequence rules (37 C.F.R. § 1.821-1.825). In this regard, a substitute "Sequence Listing" paper copy is attached in compliance with 1.825(a). It is noted that newly added SEQ ID NOs: 17-19 find support at pages 29 and 31 of the application. Accordingly, the substitute paper copy contains no new matter. In order to comply with 1.825(b), applicant has also attached the "Sequence Listing" in computer readable form. The computer readable copy is the same as the substitute copy of the "Sequence Listing."

The present response amends claims 1, 25, 27, 29 and 42. The points "(a)", "(b)" and "(c)" have been added to claims 1 and 27 to readily delineate the separate components of the pharmaceutical agent delivery composition. The addition of the "optional" intracellular delivery component to claim 1 is supported at p. 4, ll. 10-17.

Support for the negative limitations added to claims 1, 25 and 27 can be found in the positive alternative embodiments described at p. 9, ll. 22-26 in view of p. 12, l. 31- p. 13, l. 3. It is noted that these negative limitations do not constitute new matter. MPEP 2173.05(i) (citing *In re* Johnson, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977)). Support for the limitation in claims 29 and 42 of "at least about 27% of said amino acid residues of said peptide are histidine" can be found in the originally filed application at p. 23, ll. 8-9 (SEQ ID NO:7) and p. 29, ll. 8-15 in view of page 12, lines 13-15. Specifically, it is noted that about 27% of the amino acids in the Y-HK polymer (SEQ ID NO:7) are histidine. Thus, the 27% limitation finds support in a specific embodiment described in the specification and merely represents a narrowing of a specifically disclosed broader range. Accordingly, this limitation clearly is supported by the original disclosure. See MPEP 2163.05 III. Range Limitations (citing *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976)). Support for the limitation in claims 29 and 42 of "at least

about 33% of said amino acid residues of said peptide are selected from the group consisting of non-histidine residues which carry a positive charge at physiological pH" can be found in the originally filed application at p. 36, l. 8 and p. 37, l. 18 (SEQ ID NO: 15) in view of original claim 11 (now cancelled). Specifically, it is noted that about 33% of the amino acid residues in SEQ ID NO:15 carry a positive charge at physiological pH. Thus, the 33% limitation is supported on the same basis that the 27% limitation is supported.

Claims 27-52 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter not described in the specification. Claims 1-10 and 12-52 stand rejected under 35 U.S.C. 112, first paragraph, as lacking enablement support. These rejections are discussed in turn.

Written Description Rejection

Claims 27-52 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter not described in the specification (a new matter rejection). Specifically, the Examiner notes the limitation in claim 27 reciting "linear and having at least 13 amino acids"; the limitation in claims 29 and 42 reciting "at least about 86% of said amino acid residues of said peptide are selected from the group consisting of non-histidine residues"; and the limitation in claims 46-51 reciting "wherein at least about 27% of the amino acid residues of said peptide are histidine."

Applicant respectfully disagrees with the Examiner as to the rejection of claims 27 and 46-51. Support for "27%" of the amino acid residues being histidine was discussed above in relation to the currently amended claims. As for the limitation in claim 27, it is noted that the specification describes a linear transport polymer having a length of 13 amino acids and use thereof. See p. 26, ll. 1-9, Figure 3, and SEQ ID NO:1. Original claim 1 calls for a transport polymer (linear or branched) having at least 10 amino acids. Thus, a limitation calling for a transport polymer which is "linear and having at least 13 amino acids," merely represents an increase in the minimum size of linear transport polymers from a broader disclosed range. Since the new minimum size finds explicit support in a working embodiment, this limitation clearly has support in the specification as filed. See MPEP 2163.05 III. Range Limitations (citing *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976)).

As for claims 29 and 42, while not necessarily agreeing with the Examiner, applicant notes that the amendment of these claims obviates this rejection.

For the reasons stated above, applicant respectfully requests withdrawal of the new matter rejections.

Enablement Rejection

Claims 1-10 and 12-52 stand rejected under 35 U.S.C. 112, first paragraph, as lacking enablement support. Specifically, the Examiner states at pp. 4-5:

> With respect to the currently amended claims, the as-filed specification only teaches and contemplates that an enhanced transport of a pharmaceutical agent having an overall negative charge ... can be achieved by a histidine containing cationic peptide, which is further characterized as having the remaining non-histidine amino acid resides [sic] with a side group that carries a positive charge at physiological pH.

At pages 5-7, the Examiner asserts that the specification lacks teaching and guidance on selecting non-histidine amino acids necessary to enable a skilled artisan to produce a transport polymer which is suitable for the remaining scope of pharmaceuticals and transport polymers encompassed by the claims. In support, of this assertion, the examiner cites Midoux (U.S. Pat. No. 6,372,499), which teaches that polyhistidine is very poorly soluble in an aqueous medium at neutral pH, and that it is not capable of forming stable complexes with DNA at neutral pH. The Examiner further cites that the skilled artisan would not extrapolate predictability across the full scope of the claims based on the working examples provided in the specification. The Examiner further states that it is not apparent how the full scope of pharmaceutical agents encompassed within the scope of the claims can be associated with the transport polymers called for in the claims. Finally, at p. 8, the Examiner cites Chen *et al.* for the statement that "without liposomes the linear HK [histidine/lysine] polymer would have been discounted as a transfection carrier in both endothelial cells and fibroblast." as indicating the unsuitability of pharmaceutical delivery compositions not comprising an intracellular delivery component.

Applicants respectfully traverse this rejection.

As to the Midoux patent, Applicant directs the Examiner's attention to ¶¶ 3-7 of the attached 37 CFR 1.132 Declaration of Dr. Mixson, the sole inventor of the above application, and Exhibits A and B attached thereto. Dr. Mixson indicates that a large number of histidine copolymers have been produced without any solubility problems. See ¶¶ 4, 6-7. Based on his working experience, Dr. Mixson would expect that a peptide comprising 90% histidine residues as called for in the current claims would still be soluble. See ¶ 5.

Dr. Mixson also disagrees with the Examiner's contention that the skilled artisan would not extrapolate predictability across the full scope of the claims based on the working examples provided in the specification. ¶¶ 12 and 13. Applicant believes the Examiner has misconstrued the heart of the invention and underestimated the level of skill in the art. As indicated in the Declaration of Dr. Mixson, the method by which the histidine component of the transport polymer facilitates intracellular delivery, is *not by enhancing endocytic uptake across the cell membrane*, as posited by the Examiner, *but by buffering and facilitating release from pre-lysosomal vesicles*. See ¶ 13 of the Declaration. This is explicitly indicated in the specification at page 22, lines 19-21. See also, page 27, lines 19-30. Dr. Mixson further indicates in ¶ 13 that one of skill in the art would recognize, in particular with respect to the buffering capacity attributed solely to histidine, that the effect of the histidine copolymer is not due to the nature of the non-histidine amino acids or the physical properties of the pharmaceutical agent used in the working examples.

As for associating the full range of pharmaceutical agents encompassed within the scope of the claims with the full range of transport polymers called for in the claims, Dr. Mixson indicates that regardless of the physical characteristics of the transport polymer (as determined by the by nature of the non-histidine amino acids) and pharmaceutical agent, both the method and means used to associate a pharmaceutical agent to a histidine copolymer comprising non-histidine cationic amino acid residues would be obvious to those knowledgeable in the art of organic and medicinal chemistry. See ¶¶ 9-10. In this regard, applicant notes that the specification specifically teaches at p. 13, ll. 8-14, that the non-histidine amino acids are selected so as to tailor the transport polymer to the particular pharmaceutical agent and the intended method of association. See also, ¶ 14 of Dr. Mixson's declaration. The specification further teaches that if covalent association is used, the selection of non-histidine amino acids is less restricted. In fact, at p. 17, ll. 2-3, the specification expressly states that for pharmaceutical agents other than nucleic acid, covalent association is the preferred method of associating the transport polymer and the pharmaceutical agent.

Dr. Mixson further indicates that covalent coupling means are well known in the art. See ¶ 9. Dr. Mixson further points out that consistent with what is known in the art on coupling methods, the specification teaches (p. 13, ll. 12-15) that covalent bonding of a pharmaceutical

agent to a transport polymer is always available as a method for associating these two components and means for accomplishing this are well known in the art. See ¶¶ 9 and 11.

As regards the nature of the non-histidine amino acids, Dr. Mixson asserts that it would be apparent to a skilled artisan based on the specification in view of the knowledge in the art, that the selection of non-histidine amino acids is most directly relevant to whether the pharmaceutical delivery composition comprises an intracellular delivery component. See ¶ 15. Applicant notes that the specification teaches a number of intracellular delivery components, including liposomes and micelles. See pages 15-16 of the specification. Dr. Mixson states that it would readily be apparent to the skilled artisan based on the physical properties of the transport polymer, pharmaceutical agent, and associated complex thereof, whether an intracellular delivery component would be required. See ¶ 16. Dr. Mixson further states that methods for preparing and using liposomes and micelles to deliver pharmaceutical agents (whether anionic, cationic, neutral, hydrophilic or hydrophobic) were well known in the art as of the filing date of the present application. ¶ 15 of Dr. Mixson's declaration.

In support of Dr. Mixson's statement, Applicant's attorney directs the Examiner's attention to the fact that as of December, 2004, more than *2182* patents have issued which are classified under U.S. Class 424/450, which relates to the use of liposomes to deliver pharmaceutical agents. A good deal of these patents teach generic methods for preparing liposomes containing a generic class of pharmaceutical agents. See, for example, U.S. Pat. No. 5,776,486 (Castor, *et al.*), entitled "Methods and apparatus for making liposomes containing hydrophobic drugs." Applicant further notes that a search of the PTO patent database indicates that 474 of these patents issued prior to 11/5/01 with claims reciting "peptide(s)", "protein(s)" or "polypeptide(s)."

Finally, as to the Examiner's citation to Chen *et al.* as indicating the unsuitability of pharmaceutical delivery compositions not comprising an intracellular delivery component, Dr. Mixson (the senior author in the Chen paper) indicates that this statement was made in the context of comparing a linear histidine copolymer with the combination of linear histidine copolymer and liposome as regards *commercial* utility and would have been understood in this manner by one of skill in the art. See ¶ 17. Dr. Mixson further asserts that the statement would not have been interpreted as indicating that a linear or branched histidine copolymer "by themselves" would not have any effect. See ¶ 17. In support of Dr. Mixson's assertions,

Applicant further notes that the ability of a cationic polymer to enhance cellular uptake of a pharmaceutical agent, regardless of the nature of the pharmaceutical agent, is already known in the art. Specifically, Applicant directs the Examiner's attention to U.S. Pat. No. 4,847,240 (identified in the Information Disclosure Statement submitted with the present response). The '240 patent teaches covalently attaching a wide variety of molecules to a cationic polymer to increase cellular uptake thereof. See col. 5, ll. 47-63. Applicant further directs the Examiner's attention to claims 7-15 and 21-25 of the '240 patent. Applicant still further directs the Examiner's attention to col. 9, ll. 19-23 of the '240 patent, which indicates that those "skilled in the art will recognize, or be able to determine using no more than routine experimentation ... suitable conjugation mechanisms to covalently bond a specific molecule to be transported into cells to a specific cationic polymer chosen as a transport carrier." Finally, Applicant directs the Examiner's attention to the fact the claims in the '240 patent issued from a divisional application of an application filed in 1979. Applicant submits that since the art has not become less predictable in the last 25 years, the use of linear cationic histidine copolymers with the full scope of pharmaceutical agents encompassed within the presently amended claims is fully enabled.

Finally, Applicant notes that claim 1 has been amended to recite the optional use of an intracellular delivery component. Dr. Mixson indicates that in view of the fact that all of the claims recite an optional intracellular delivery component (ex. liposomes), that regardless of the physical properties of the transport polymer and pharmaceutical agent, a skilled artisan could prepare without undue experimentation the full scope of pharmaceutical agent delivery compositions encompassed within the currently amended claims.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance; however, if the Examiner disagrees, the applicants respectfully request that the Examiner telephone the undersigned at (302) 888-6210.

A one month extension fee has been paid. Applicant notes that a one month extension of the original three month period, which ended 11/25/04, makes this response timely if filed on or before December 27, 2004, since the last day for response is Friday 12/25/04, a Federal holiday. If there are any additional fees due in connection with the filing of this response, including any fees required for an additional extension of time under 37 CFR 1.136, such an extension is

requested and the Commissioner is authorized to charge any debit or credit any overpayment to Deposit Account No. 03-2775, under Order No. 05627-00005-USA from which the undersigned is authorized to draw.

Dated: December 20, 2004

Respectfully submitted,

By Gary A. Bridge

Gary A. Bridge
Registration No.: 44,560
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P.O. Box 2207
Wilmington, Delaware 19899
(302) 658-9141
(302) 658-5614 (Fax)
Attorney for Applicant